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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/718,185	11/19/2003	Shripad S. Bhagwat	10624-143-999	9314

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EXAMINER	
CLAYTOR, DEIRDRE RENEE	
ART UNIT	**PAPER NUMBER**
1617	

MAIL DATE	DELIVERY MODE
10/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/718,185	BHAGWAT ET AL.	
	Examiner	Art Unit	
	Renee Claytor	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 August 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above claim(s) *4,6 and 18-25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5 and 7-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/19/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restriction

Applicant's election of Group I, claims 1 (in part), 2, and 3-25 (in part) in the reply filed on 7/5/2007 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Applicant's election of 3-(3-(2-piperidin-1-yl)ethoxy)phenyl)-5-(1H-1,2,4-triazol-3-yl)-1H-indazole and cancer as the species is further acknowledged. Accordingly, the claims are being examined as they read on the elected species and claims 1-3, 5 and 7-17 are being examined on their merits herein.

The requirement is still deemed proper and is therefore made FINAL.

Priority

Since the parent applications, 09/910,950 and 10/414,839, have become patents, please update the first line of the specification to indicate that.

Claim Rejections – 35 U.S.C. § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5, and 7-17 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which

was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. "The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546.

1) The nature of the invention and breadth of the claims: The nature of the invention and breadth of the claims is drawn to a method for treating or preventing a disease (cancer) comprising administering an effective amount of a compound having the structure in claim 1 (in particular the elected species 3-(3-(2-(piperidin-1-yl)ethoxy)phenyl)-5-(1H-1,2,4-triazol-3-yl)-1H-indazole).

2) The presence or absence of working examples and the amount of direction or guidance presented: In the instant case, working examples are presented for measuring the activity of the compounds of the invention in various assays, such as JNK2 assay, JNK3 assay, Jurkat T-cell 11-2 Production Assay, rat in vivo LPS-induced TNF-α Production assay and various other assays (see Examples

435-509). These assays verified the ability of the compounds to inhibit the various receptors and their corresponding IC50 value. However, there is no data exemplifying treatment of any type of cancer with the compounds of the invention.

The extent of the studies of the present invention is to determine the activity of the various indazole compounds of the invention in inhibiting tyrosine kinase signal transduction. This determination is done via various protein kinase assays. The determination of a particular claimed compound in the treatment of cancer requires the synthesis of the compound, formulation into a suitable dosage form, and testing in a known assay that is correlated with clinical efficacy. Applicants state on pages 40-42 that the compounds of the invention are useful in treating cancer and list various cancers that can be treated. However, there are no further examples exemplifying the effectiveness of the compounds in an animal model of any particular cancer with no effective dose range being determined in the treatment of cancer.

The issue in *Ex parte Balzarini* 21 USPQ2d 1892 concerned HIV treatment and the Board of Patent Appeals and Interferences wrote "while the *in vitro* testing performed on these anti-viral compound appears to be useful as a screening tool in order to determine which of these anti-viral compounds are candidates for further testing to determine if they possess *in vivo* utility, the *in vitro* tests were not predictive of *in vivo* efficacy". Furthermore, the issue in *Fujikawa v. Wattanasin* 39 USPQ2d 1895 was adequacy of *in vitro* testing of inhibitors of cholesterol biosynthesis and U.S. Court of Appeals Federal Circuit wrote, "*in vitro* results, in combination with a known correlation between such *in vitro* results and *in vivo* activity, may be sufficient to

establish practical utility". A working example in *in vivo* experiments showing that the compounds would effectively treat the claimed diseases is lacking.

3) The state of the prior art: The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling. >See, e.g., Chiron Corp. v. Genentech Inc., 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004).

Substantiation of use and scope is required when the use is "speculative", "sufficiently unusual" or not provided in the specification, *Ex parte Jovanovics*, 211 USPQ 907, *In re Langer*, 183 USPQ 288, *Hoffman v. Klaus*, 9 USPQ2d 1657, and *Ex parte Powers*, 200 USPQ 925 concerning the type of testing needed to support *in vivo* use claims. Also see MPEP § 2164.03 for enablement requirements in the structure sensitive arts of pharmacology and medicinal chemistry.

It is art recognized that a perturbation of protein tyrosine kinase (PTK) activity results in a variety of diseases, including cancer (see Al-Obeidi et al., Oncogene (2000) 19, 5690-5701). In the Introduction of this paper, it is stated that many PTK's have been implicated in human cancer and give examples of some specific PTK's that are implicated in different types of cancer. Al-Obeidi et al. goes on to discuss the

approaches to the development of inhibitors and discusses compounds that have been tested in pre-clinical and clinical studies. Al-Obeidi et al. discusses that inhibitors of some PTK's may be useful for the treatment of a number of diseases and that a large number of PTK inhibitors have been developed and that several are undergoing clinical trials. Al-Obeidi et al. conclude that it is likely that several clinically useful PTK inhibitors will be on the market within the next decade, making it evident that not all of the PTK inhibitors that will be synthesized will necessarily be effective in clinical situations and should be tested.

4) The quantity of experimentation necessary: "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed Cir. 1993)". Undue experimentation would be required in order to practice Applicant's invention because there are no examples provided in the specification in an approved animal model for any type of cancer with any indazole compound and in particular the elected compound 3-(3-(2-(piperidin-1-yl)ethoxy)phenyl)-5-(1H-1,2,4-triazol-3-yl)-1H-indazole. One would have to determine a useful model that correlates with clinical efficacy, a dosage range would need to be determined as well as a route of administration. Further, if any of the above failed, then the artisan would have to start over again in an effort to determine the suitable methods, dosage ranges and routes of administration in which to determine if the compounds will work to treat cancer.

Claims 1-3, 5 and 7-17 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for determining the activity of various indazole compounds that inhibit, modulate or regulate tyrosine kinase signal transduction, does not reasonably provide enablement for the prevention of all cancers with the indazole compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant specification fails to provide information that would allow the skilled artisan to practice the instant invention without undue experimentation. Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

1) The nature of the invention and breadth of the claims: The nature of the invention and breadth of the claims is drawn to a method for treating or preventing a disease (cancer) comprising administering an effective amount of a compound having the structure in claims 1 (in particular 3-(3-(2-(piperidin-1-yl)ethoxy)phenyl)-5-(1H-1,2,4-triazol-3-yl)-1H-indazole).

2) The presence or absence of working examples and the amount of direction or guidance presented: : In the instant case, working examples are presented for measuring the activity of the compounds of the invention in various assays, such as JNK2 assay, JNK3 assay, Jurkat T-cell 11-2 Production Assay, rat in vivo LPS-induced TNF-α Production assay and various other assays (see Examples 435-509). These assays verified the ability of the compounds to inhibit the various receptors and their corresponding IC50 value. However, there is no data exemplifying treating or preventing all types of cancer with the compounds of the invention. There is no data presented in accepted animal models of various types of cancer suggesting that indazole compounds would show clinical efficacy in treating or preventing all cancers.

3) The state of the prior art: The state of the art for the treatment of various types of cancer is high. However, the state of the art for the prevention of cancer is underdeveloped.

4) The quantity of experimentation necessary: "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed Cir. 1993)". Undue experimentation would be required in order to practice Applicant's invention because there are no examples provided in the specification showing that all cancers would be treated or prevented following administration of indazole compounds. Applicant fails to provide information sufficient to practice the claimed invention, absent

undue experimentation. Genetech, 108 F.3d at 1366 states that "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 15-17 rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 7,220,771. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application are drawn to a method of treating a disease (cancer) comprising administration of an indazole compound of claim 1. The

claims of US Patent 7,220,771 are drawn to a method for treating cancer of the blood, brain, lung or prostate comprising administration of an indazole compound with the same core structure as the instant application. Though all of the side groups are not identical between the applications, one would have a reasonable expectation of success that because the compounds share the same core structure, that they would both treat cancer.

Claims 1-3 and 14-17 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-2 and 9-10 of copending Application No. 11/512,836. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims are drawn to a method for treating disease (cancer) comprising administration of an indazole compound (3-(3-(2-(piperidin-1-yl)ethoxy)phenyl)-5-(1H-1,2,4-triazol-3-yl)-1H-indazole). The claims of application 11/512,836 are drawn to a method for treating chronic lymphocytic leukemia comprising administration of 3-(3-(2-(piperidin-1-yl)ethoxy)phenyl)-5-(1H-1,2,4-triazol-3-yl)-1H-indazole. The applications are obvious over the other in that they both involved treatment of a cancer with indazole compounds.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-3 and 14-17 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of copending Application No. 11/376,786. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims are drawn to a method for treating disease (cancer) comprising administration of an indazole compound (3-(3-(2-(piperidin-1-yl)ethoxy)phenyl)-5-(1H-1,2,4-triazol-3-yl)-1H-indazole). The claims of application 11/376,786 are drawn to a method for treating acute myelogenous leukemia comprising administration of 3-(3-(2-(piperidin-1-yl)ethoxy)phenyl)-5-(1H-1,2,4-triazol-3-yl)-1H-indazole. The applications are obvious over the other in that they both involved treatment of a cancer with indazole compounds.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

No claims are allowed.

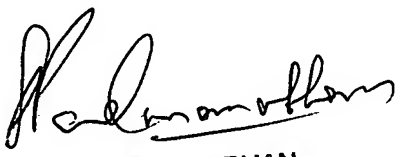
Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Renee Claytor whose telephone number is 571-272-8394. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Renee Claytor



SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER